RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

for pregnant and breastfeeding women

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	RECOVERY trial protocol	Adaption for pregnancy
Eligibility	Patients are eligible if all of the following are true: i. Hospitalised ii. SARS-CoV-2 infection iii. No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial	Same eligibility
Interventions	**First randomisation** • No additional treatment • Azithromycin • Convalescent plasma **Second randomisation** • Tocilizumab	Same interventions
Follow-up/ outcomes	Ascertained at the time of death or discharge or at 28 days after randomisation (whichever is sooner): ➢ Vital status (alive/ dead, with date and presumed cause of death, if appropriate) ➢ Hospitalisation status (inpatient/ discharged, with date of discharge, if appropriate) ➢ Use of ventilation (none/ previous/ ongoing, with days of use and type, if appropriate) ➢ Use of renal dialysis or haemofiltration (none/ previous/ ongoing)	Same follow-up and outcomes, with addition of UKOSS COVID-19 case number (for pregnancy and baby information) to allow later data linkage
		Adaptions for breastfeeding
		The same interventions should be used. UKOSS COVID-19 case number added if available.

Frequently asked questions

1. **Are the drugs safe in pregnancy?** The pregnancy leads for the trial have reviewed the safety literature (Annex A), and experience around using these drugs for other conditions, and consider that participation in the trial is reasonable for pregnant and breastfeeding women. The regulators (MHRA and HRA) have agreed to the inclusion of pregnant women.
2. **Where can I find information specifically written for pregnant women about the drugs?**
   The links below are provided with permission from the bumps (best use of medicines in pregnancy) website, who have developed information leaflets for each of the drugs used in the RECOVERY trial. The bumps website and information are provided by the UK Teratology Information Service (UKTIS), a not-for-profit organisation funded by Public Health England on behalf of the UK Health Departments.
   - Azithromycin: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Azithromycin/
   - Tocilizumab: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Tocilizumab/
3. **Who has endorsed the trial?** The trial itself has been endorsed by the **Chief Medical Officer and NHS England Medical Director.** Inclusion of pregnant and postpartum women has been endorsed by NHS England, the Royal College of Obstetricians and Gynaecologists, Royal College of Midwives, Royal College of Physicians, Tommy's Charity, British Maternal and Fetal Medicine Society, Macdonald Obstetric Medicine Society, the Neonatal Society, the Reproductive Health and Childbirth Specialty Group Lead (NIHR Clinical Research Network).
4. **Who should take consent for inclusion in the trial?** Any healthcare professional with appropriate training and knowledge of the trial can take consent. Obstetricians, obstetric physicians and midwives can make their colleagues aware that pregnant and postpartum women are eligible for the trial and should be approached for participation. Consent does not need to be taken specifically by an obstetrician, obstetric physician or research midwife. **RECOVERY Information for site staff**
5. **Can I offer the trial to a woman who is in hospital for another reason?**
   If you are looking after a woman with a positive covid-19 swab result who was initially admitted for another reason (e.g. in labour), ask whether you are uncertain about the benefits of treatment or not for this woman, either for treatment or to prevent deterioration. If you are uncertain, then it is reasonable to provide the information to the woman, offer the trial and make a shared decision. We do not know what is the optimal time to offer treatment.

6. **Who collects the outcome data?** The outcome data will be collected as usual for the trial, with the exception of pregnancy-specific data, which will be collected by research nurses or research midwives as part of the ongoing **UKOSS COVID-19 study in pregnancy,** using the **UKOSS COVID-19 Data Collection Form.** All pregnant women should be reported within the UKOSS COVID-19 study (although this does not need to be started before consent to RECOVERY), and the UKOSS number should be included in the outcome data.
7. **Can we give women corticosteroids for fetal lung maturity?** Yes, if indicated, as in usual clinical obstetric practice (see **RCOG guidance in COVID-19 pandemic**)
8. **Can we take part?** Any hospital that has R&D approval for RECOVERY can take part. There are no special approvals needed for including pregnant and breastfeeding women. A 'pregnancy lead' healthcare professional will be identified, to work alongside the site Principal Investigator.

Annex A: Trial drugs in pregnancy and during lactation

All trial drugs have been used in pregnant women with pre-existing medical disorders where benefits outweigh the risks to fetus or woman, including in the first trimester. The existing data related to each drug is summarized below.

Azithromycin

Azithromycin is used in pregnancy to treat genital Chlamydia trachomatis infection, with a Cochrane systematic review and meta-analysis reporting fewer gastrointestinal side-effects compared to erythromycin, and inconsistent results on risk of preterm birth, preterm rupture of membranes, perinatal mortality and low birthweight, confounded by the indication for treatment.[1] A recent systematic review and meta-analysis of all macrolide antibiotics acknowledges potential bias in child outcome reports due to treatment indication.[2] The UK Teratology Information Service monograph concludes that there is no definitive evidence linking azithromycin with increased risk of miscarriage or congenital malformations (https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-MACROLIDES-IN-PREGNANCY/). Azithromycin is detected in only low levels in breastmilk and is not expected to cause adverse events in breastfed infants (reviewed in Lactmed database: www.ncbi.nlm.nih.gov/books/NBK501200/) Azithromycin has also been used in several trials in preterm infants as a prophylactic treatment to prevent bronchopulmonary dysplasia.[3]

Additional randomisation intervention: Convalescent plasma (prepared with Dr Sue Pavord, Consultant Haematologist)

Convalescent plasma is plasma from people who had confirmed COVID-19 (SARS-Cov-2) infection, and have now recovered and been free of the infection for 28 days. The plasma contains antibodies that their immune systems have produced in fighting the virus. It is hoped that giving this plasma will help speed up recovery of a patient with active infection and improve their chances of survival. Plasma is already used as a treatment in pregnant patients who are bleeding,[4] or have particular blood conditions.[5, 6] The plasma being used in this trial is from a selected donor and hopefully contains anti-SARS-Cov-2 antibodies, but is otherwise no different. Plasma infusions can occasionally cause side effects. Mostly this is a rise in temperature, itching or a rash, and in very extreme cases, anaphylaxis. Other potential complications include breathlessness and changes in blood pressure. Monitoring of pulse and blood pressure takes place before and after the infusion. There is no risk of miscarriage or fetal loss, preterm birth, preterm rupture of membranes, perinatal mortality or low birthweight, from plasma transfusions and there are no concerns with breast feeding.

Second randomisation intervention: Tocilizumab

Two pharmaceutical global safety registry database studies have reported on tocilizumab use in pregnancy, including outcomes from 288 pregnancies [7] and 61 pregnancies,[8] typically for rheumatoid or other arthritides, and with the majority having received the drug in the first trimester. These data suggest that the rates of congenital abnormality, spontaneous pregnancy loss and other adverse outcomes were not higher than in the general population.[8] Small studies have shown that tocilizumab is transferred to the fetus with serum concentrations approximately 7-fold lower than those observed in maternal serum at the time of birth.[9] Very low concentrations of tocilizumab are identified in breast milk and no drug is transferred into the serum of breast fed infants.[9, 10] Women should be advised that if treated after 20 weeks' gestation, their infant should not be immunised with live vaccines (rotavirus and BCG) for the first 6 months of life. All non-live vaccinations are safe and should be undertaken.[11]

References

1. Cluver, C., et al., *Interventions for treating genital Chlamydia trachomatis infection in pregnancy.* Cochrane Database Syst Rev, 2017. **9**: p. CD010485.
2. Fan, H., et al., *Associations between use of macrolide antibiotics during pregnancy and adverse child outcomes: A systematic review and meta-analysis.* PLoS One, 2019. **14**(2): p. e0212212.

3. Nair, V., P. Loganathan, and A.S. Soraisham, *Azithromycin and other macrolides for prevention of bronchopulmonary dysplasia: a systematic review and meta-analysis.* Neonatology, 2014. **106**(4): p. 337-47.
4. Townsley, D.M., *Hematologic complications of pregnancy.* Semin Hematol, 2013. **50**(3): p. 222-31.
5. Brooks, J.P., et al., *Experience with Intravenous Plasma-Derived C1-Inhibitor in Pregnant Women with Hereditary Angioedema: A Systematic Literature Review.* J Allergy Clin Immunol Pract, 2020.
6. Scully, M., et al., *Thrombotic thrombocytopenic purpura and pregnancy: presentation, management, and subsequent pregnancy outcomes.* Blood, 2014. **124**(2): p. 211-9.
7. Hoeltzenbein, M., et al., *Tocilizumab use in pregnancy: Analysis of a global safety database including data from clinical trials and post-marketing data.* Semin Arthritis Rheum, 2016. **46**(2): p. 238-245.
8. Nakajima, K., et al., *Pregnancy outcomes after exposure to tocilizumab: A retrospective analysis of 61 patients in Japan.* Mod Rheumatol, 2016. **26**(5): p. 667-71.
9. Saito, J., et al., *Tocilizumab during pregnancy and lactation: drug levels in maternal serum, cord blood, breast milk and infant serum.* Rheumatology (Oxford), 2019. **58**(8): p. 1505-1507.
10. Saito, J., et al., *Tocilizumab concentrations in maternal serum and breast milk during breastfeeding and a safety assessment in infants: a case study.* Rheumatology (Oxford), 2018. **57**(8): p. 1499-1501.
11. Flint, J., et al., *BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids.* Rheumatology (Oxford), 2016. **55**(9): p. 1693-7.